IV Antibiotics Potentiator Platform for Treating MDR Gram-Negative Infections in the Hospital

There has been a significant decrease in the number of novel IV antibiotics in development and approved over the past 40 years for the treatment of Gram-negative infections. The physiology of Gram-negative bacteria – specifically the make-up of the outer-membrane of these bacteria – is one of the primary roadblocks hindering innovation.

While Gram-positive bacteria possess a single phospholipid cell membrane, Gram-negative bacteria have a phospholipid inner membrane (akin to the Gram-positive membrane), plus an outer membrane bilayer composed primarily of phospholipid at the inner surface and lipopolysaccharide (LPS) at the outer leaflet. It is this layer of highly polar, negatively charged LPS that excludes many excellent target-based inhibitors, including a trove of clinically useful Gram-positive antibiotics from entering Gram-negative bacteria to do their work.

Unfortunately, a distinct incongruence between chemical properties required for Gram-negative penetration (both membranes), and that imposed by many of the known (and novel) bacterial targets, means that simple (or complex) medicinal chemistry tactics have not been able to provide a solution. Spero Therapeutics believes its IV Potentiator Platform approach (SPR741 & SPR206) to LPS disruption will be the solution.

About SPR741

SPR741 is an IV product that does not have any significant antimicrobial activity on its own. However, when combined with an antibiotic, SPR741 has demonstrated the ability to expand the spectrum and potency of the co-administered antibiotic against Gram-negative bacteria, including organisms identified by the CDC and WHO as urgent and serious threats. SPR741 has demonstrated the ability to expand the spectrum and enhance the potency of more than two dozen existing antibiotics and enabled expanded utility against resistant Gram-negative pathogens. SPR741 has completed Phase 1a and 1b trials highlighting its tolerability and pharmacokinetic profile.

About SPR206

Our next generation Potentiator molecule – SPR206 – is an IV direct-acting antibiotic that has shown antibiotic activity against *Acinetobacter baumanii* and *Pseudomonas aeruginosa* in preclinical studies. SPR206 completed non-clinical, IND-enabling studies supporting its advancement as a clinical candidate designed to treat MDR and extensively drug-resistant (XDR) bacterial strains.

- Potential to expand the potency of standard-of-care antibiotics.

We believe SPR741 has the potential to expand the potency of standard-of-care antibiotics by restoring and expanding their potency against resistant Gram-negative bacteria, thereby improving therapeutic outcomes, decreasing physicians' reliance on drugs of last resort and encouraging improved antibiotic stewardship.

- Broad applicability of the IV Potentiator Platform.

  We have seen in preclinical studies that our potentiators are capable of potentiating the activity of many generic and novel antibiotics from various classes. In multiple animal models of varying infection types, this potentiation effect has resulted in a significant reduction in the bacterial burden of infections caused by several common drug-resistant pathogens, including *E. coli*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*.

- Our lead potentiator molecule has a proven record of being well tolerated.

  Data from our Phase 1 SAD/MAD clinical trial of SPR741 demonstrate SPR741 was well tolerated at single doses up to and including 800 mg and multiple daily doses up to and including 600 mg every eight hours for 14 consecutive days.

- Our next-generation molecule, SPR206, may potentially be a safe and potent IV-administered direct-acting agent.

  Like SPR741, our next-generation potentiator candidate, SPR206, is designed to interact with LPS to disrupt the outer membrane. However, SPR206 is designed to have direct antibiotic activity as well, including activity against *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.